v-CJD

Dr. Kondi Wong

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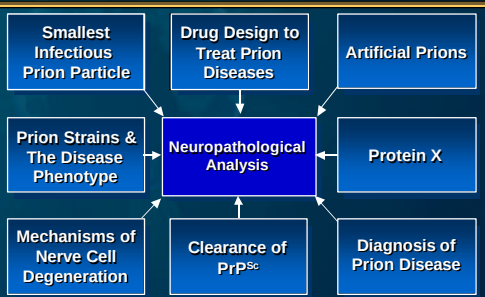
Kondi Wong, M.D.

Armed Forces Institute of Pathology

Neuropathology Provides Independent Evidence for the Prion Hypothesis



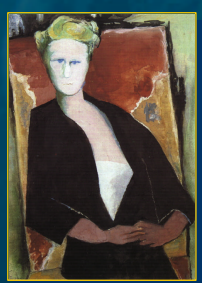
01M-02192 Wong

Human Prion Diseases

Manifestation	*Disease*	*Mechanism*
Infectious	Kuru	Transmission
	Iatrogenic CJD	
	Variant CJD	
Sporadic	Sporadic CJD	Somatic mutation or spontaneous PrP^{C} - - - > PrP^{Sc}
	Sporadic FI	
Inherited	Gerstmann-Straussler-Scheinker syndrome	Germline mutation
	Familial CJD	
	Familial FI	

01M-02193 Wong

Creutzfeldt-Jakob Disease



1920-23: First descriptions of sporadic CJD (sCJD)

1924: First description of familial CJD (fCJD)

1968: Transmission of sCJD to non-human primates

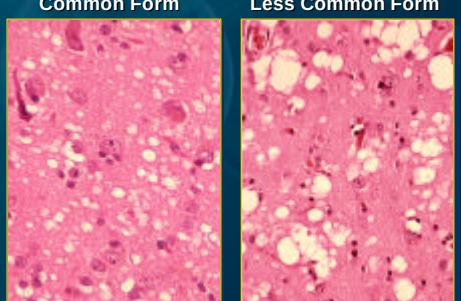
1981: Transmission of fCJD to non-human primates

1985ff: Linkage of fCJD pedigrees to mutations of the *PRNP* gene

01M-02194 Wong

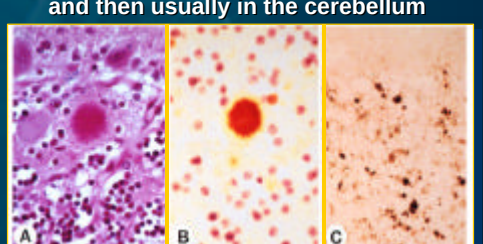
Creutzfeldt-Jakob Disease

Common Form | Less Common Form



01M-02195 Wong

Small numbers of Kuru-type amyloid plaques occur in only 5% of CJD cases and then usually in the cerebellum

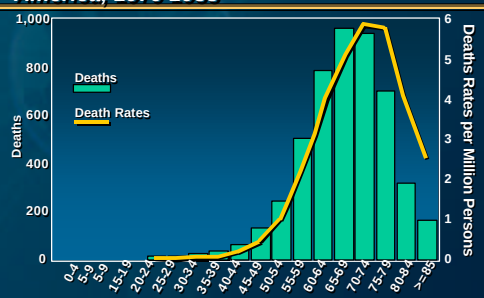


PAS *PrP* *PrP Low Power*

Creutzfeldt-Jakob Disease

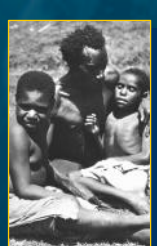
01M-02196 Wong

Cruetzfeldt-Jakob Disease Deaths and Death Rates by Age Group, United States of America, 1979-1988



01M-02197 Wong

Kuru



- Post WWII: Discovered in Fore people of New Guinea
- 1959: Clinical, neuropathological and epidemiological description complete
- 1959: Similarity to scrapie recognized
- 1966: Transmitted to non-human primates
- Transmission among the Fore by ritualistic cannibalism

01M-02198 Wong

Scrapie

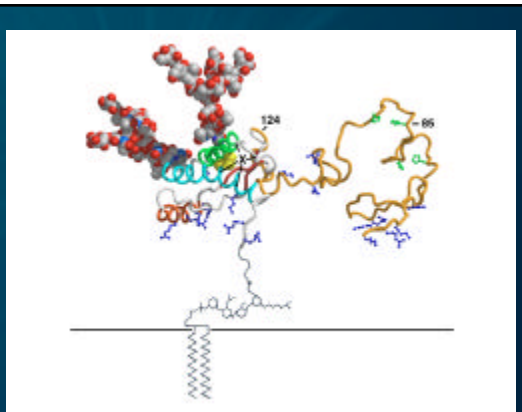
- 1743 - Recorded in Parliament
- 1938 - Transmission to goats
- 1967 - Properties atypical for a virus
- 1982 - Purified scrapie agent is a protein
- 1982 - Prion hypothesis (Prusiner)
- 1995 - Susceptibility to scrapie linked to *Prnp* gene

01M-02199 Wong

PrP^{Sc} Is the Sole Functional Component of Prions

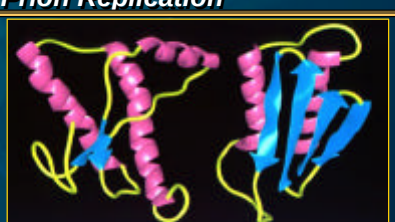
- Purified scrapie agent is composed mostly of PrP^{Sc}
- Procedures which denature proteins attenuate infectivity
- Procedures which denature nucleic acids have no effect on infectivity
- Purified prions contain small fragments of nucleic acid and no viral nucleic acid
- PrP null mice do not form prions

01M-021910 Wong



01M-021911 Wong

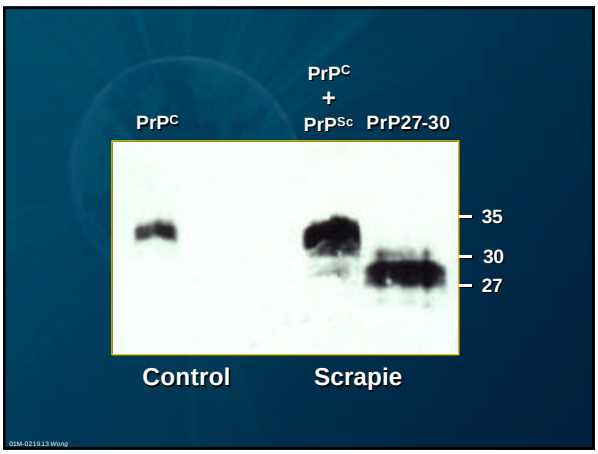
Conformational Changes Feature in Prion Replication

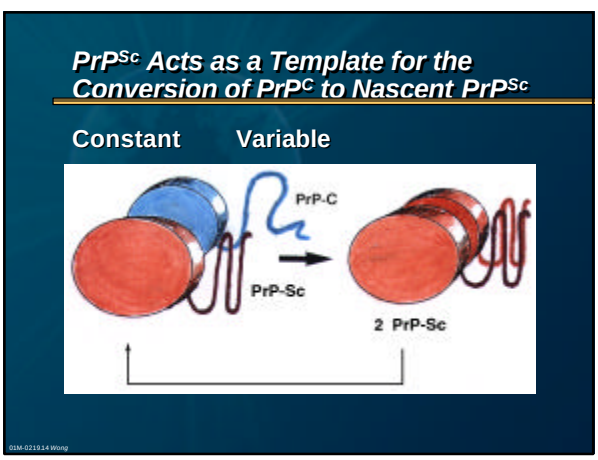


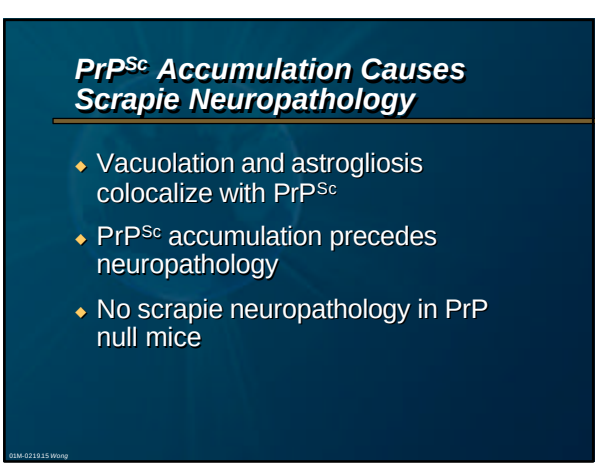
Secondary Structure (%)

42	a-helix	30
3	b-sheet	43
Negative	Scrapie infectivity	Positive

01M-021912 Wong


PrP^C
PrP^C + PrP^Sc
PrP27-30
35
30
27
Control
Scrapie
01M-021913 Wong

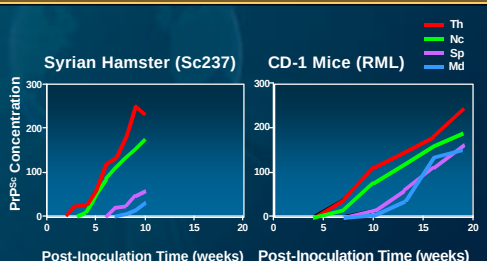

PrP^Sc Acts as a Template for the Conversion of PrP^C to Nascent PrP^Sc
Constant
Variable
PrP-C
PrP-Sc
2 PrP-Sc
01M-021914 Wong


PrP^Sc Accumulation Causes Scrapie Neuropathology
Vacuolation and astrogliosis colocalize with PrP^Sc
PrP^Sc accumulation precedes neuropathology
No scrapie neuropathology in PrP null mice
01M-021915 Wong

Kinetics of PrP^{Sc} Accumulation in CD1 Mice Inoculated with RML Prions Revealed by Histoblots

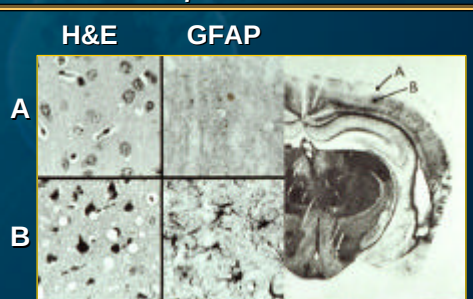
01M-021916 Wong

Kinetics of PrP^{Sc} Accumulation Following Intrathalamic Inoculation with Prions inTwo Animal Models of Scrapie



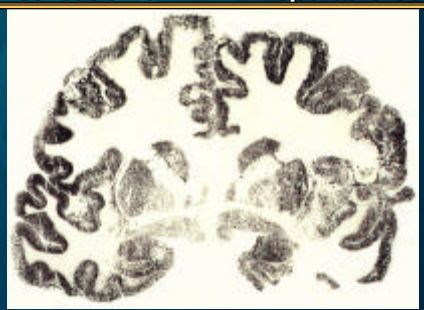
01M-021917 Wong

Neuropathological Changes Colocalize with Sites of Prp^{Sc} Accumulation



01M-021918 Wong

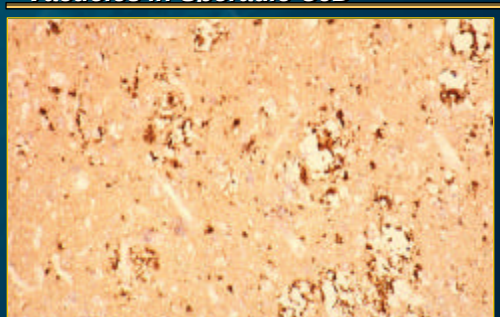
Distribution of PrP^{Sc} in Sporadic CJD



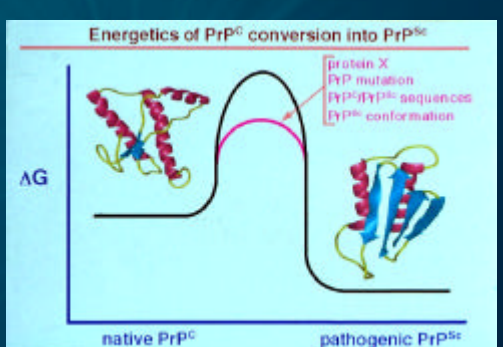
(Histoblot technique)

01M-021919 Wong

Coarse Prp^{Sc} Deposits Around Vacuoles in Sporadic CJD



01M-021920 Wong



01M-021921 Wong

Human Prion Diseases

- Sporadic (Idiopathic) (90%)
  - Sporadic Creutzfeldt-Jakob disease (sCJD)
  - Sporadic fatal insomnia (SFI)
- Dominantly Inherited (Genetic) (10%)
  - Familial CJD (fCJD)
  - Gerstmann-Sträussler-Scheinker syndrome (GSS)
  - Familial fatal Insomnia (FFI)
- Acquired by Prion Infection (< 1%)
  - Iatrogenic CJD (iCJD)
  - Kuru
  - New variant CJD (vCJD) in Europe

01M-021922 Wong

Familial Prion Diseases

1924: First fCJD pedigree described

1936: Gerstmann-Straussler-Scheinker syndrome (GSS) first described in Austrian family

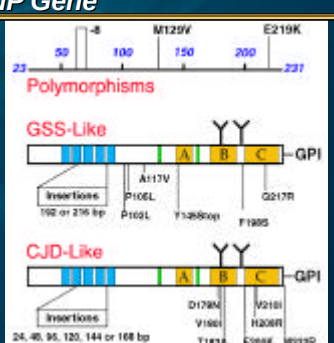
1985: Codon 102 mutation of the *PRNP* gene linked to GSS

1992: Fatal familial insomnia (FFI) added to list of familial prion diseases

All are dominantly inherited. All are linked to mutations of the *PRNP*

01M-021923 Wong

PRNP Gene



01M-021924 Wong

Two Categories of Prion Disease

1. CJD/FI/Kuru/Scrapie/BSE Group

- Spontaneous, acquired, and genetic forms
- Conversion of PrP^{C} to PrP^{Sc}
- Progressive accumulation of protease-resistant PrP^{Sc}
- Vacuolar degeneration with variable PrP amyloid
- High transmission rate

01M-021925 Wong

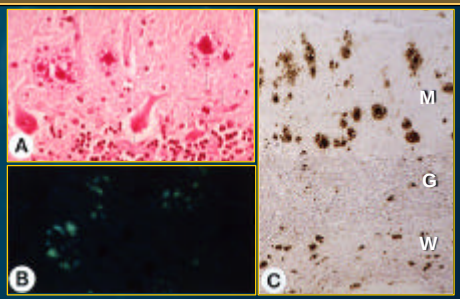
Two Categories of Prion Disease (Cont'd)

2. Gerstmann-Sträussler-Scheinker syndrome Group

- Dominantly inherited only
- Mutation yields transmembrane PrP topography
- Accumulation of protease-sensitive muPrP
- Abundant PrP amyloid, variable vacuolation
- Poor transmission rate

01M-021926 Wong

Neurpathological Features of GSS(P101L)



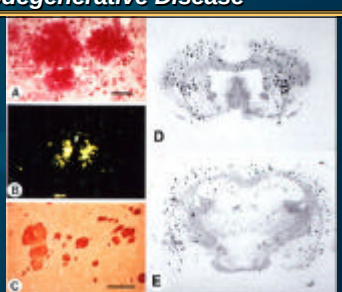
01M-021927 Wong

Tg(GSS) Mice

- Express MoPrP with P101L mutation
- Low expressors do not develop neurodegenerative disease spontaneously
- High expressors spontaneously develop cerebral amyloidosis resembling human GSS
- Clinically ill high expressors spontaneously form prions

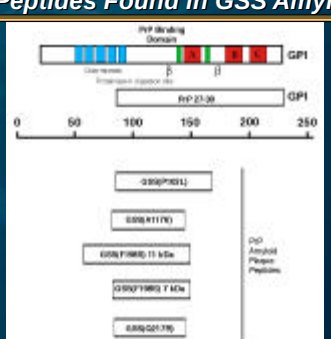
01M-021928 Wong

Tg(PrP-P101L) High Expressor Mice Spontaneously Develop a GSS-Like Neurodegenerative Disease



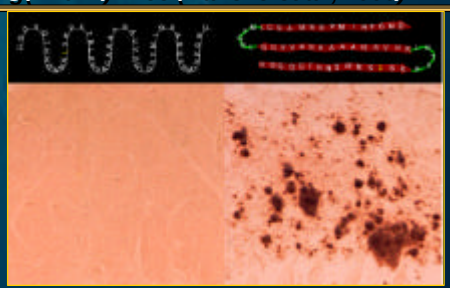
01M-021929 Wong

PrP Peptides Found in GSS Amyloids



01M-021930 Wong

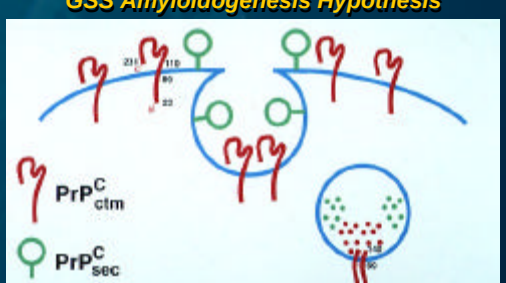
Synthetic Beta-MoPrP(89-143) with P101L Substitution Causes GSS in Tg(P101L) Mice (Kaneko et al., 1999)



01M-021931 Wong

How Can Mutated PrP in GSS be Protease-Sensitive and Amyloidogenic?

GSS Amyloidogenesis Hypothesis



01M-021932 Wong

Human Prion Diseases

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  - Sporadic Creutzfeldt-Jakob disease (sCJD)
  - Sporadic fatal insomnia (SFI)
- Dominantly Inherited (Genetic) (10%)
  - Familial CJD (fCJD)
  - Gerstmann-Sträussler-Scheinker syndrome (GSS)
  - Familial fatal Insomnia (FFI)
- Acquired by Prion Infection (< 1%)
  - Iatrogenic CJD (iCJD)
  - Kuru
  - New variant CJD (vCJD) in Europe

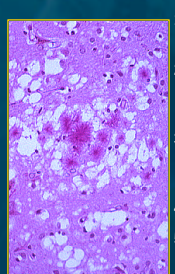
01M-021933 Wong

As scientists probe mad cow link, mother mourns a young life

CJD KILLED MY LOVELY DAUGHTER

01M-021934 Wong

New Variant of CJD in UK

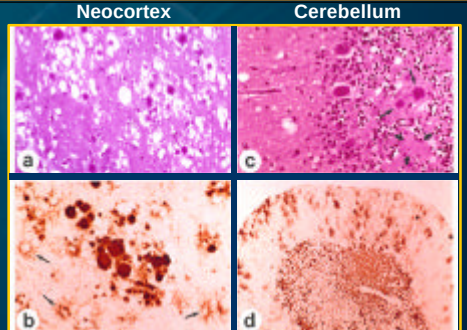


1. 1984-1985, 10 young patients (ages <40) developed atypical CJD
2. Presented with psychiatric plus sensory abnormalities, then motor abnormalities and late dementia
3. Neuropathological changes were unique for the abundance of kuru plaques in the cerebral cortex
4. No mutations of *PRNP* gene
5. Three additional cases in 1996, one in France (26, 29, 50 years old)

01M-021935 Wong

New Variant of CJD

Neocortex Cerebellum



01M-021936 Wong

Bovine Spongiform Encephalopathy

1970's: Change in method of renduring offal allowed scrapie to be transferred from sheep to cattle, primarily dairy cattle

1985: First cases of BSE identified

1988: Dietary supplements from rendered offal of ruminants banned

1992: Peak of epidemic in cattle (>160,000 cattle in 10 yrs)

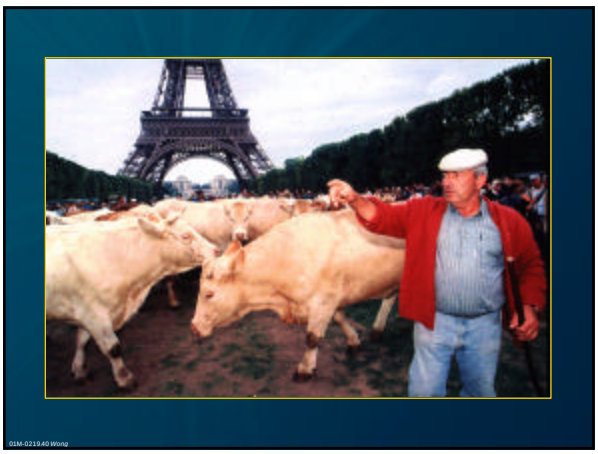
1994: First cases of a new variant of CJD appear in the United Kingdom, all in young patients

01M-021937 Wong

Bovine Spongiform Encephalopathy

01M-021938 Wong

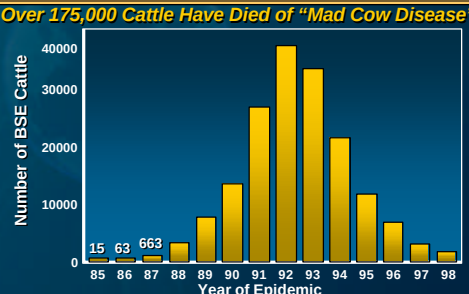
01M-021939 Wong



01M-0219.40 Wong

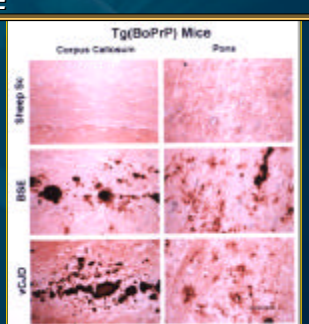
Bovine Spongiform Encephalopathy Epidemic in Great Britain

Over 175,000 Cattle Have Died of "Mad Cow Disease"



01M-0219.41 Wong

Direct Evidence That vCJD is Caused by BSE



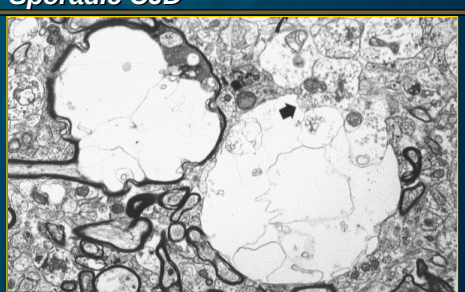
01M-0219.42 Wong

Mechanisms of Neuronal Dysfunction, Degeneration and Death

1. Both conversion of PrP^{C} to PrP^{Sc} and the accumulation of PrP^{Sc} cause neuropathology
2. Multi-subcellular compartment hypothesis
   - Subcellular distribution of PrP^{Sc}
   - Plasma membrane dysfunction
   - Endosome/lysosome dysfunction
3. Neuronal dysfunction = f([PrP^{Sc}])

01M-0219.43 Wong

Sporadic CJD



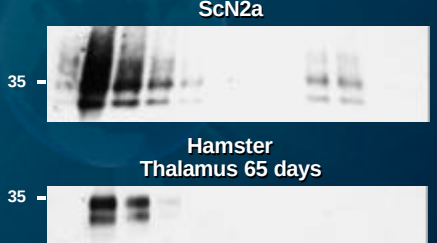
Vacuoles are within pre- and post-synaptic neuronal processes and contain abnormal membranes

01M-0219.44 Wong

More Than 90% of PrP^{Sc} is Localized to the Plasma Membrane Fractions

(Aliquots of Equal Volume Loaded)

ScN2a

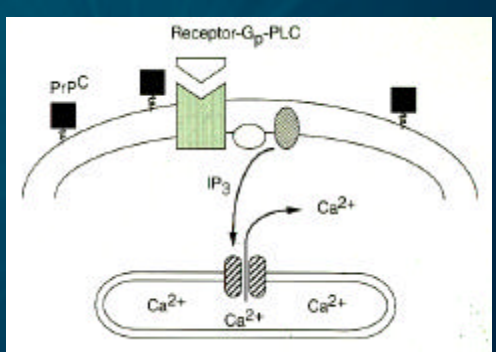


01M-0219.45 Wong

Plasma Membrane Abnormalities in Prion Infected Cell Lines

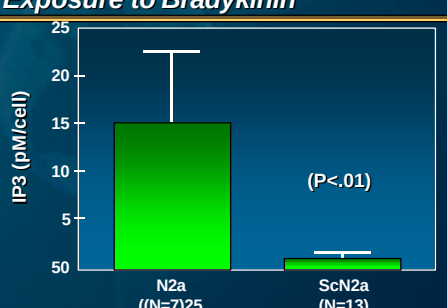
	ScN2a	ScGT
PrP^{Sc} in Plasma Membrane	↑ 15 fold	↑ 15 fold
Membrane Fluidity	↓ 7 fold	ND
Bk-Stimulated Ca^{2+}	↓ 60%	ND
Bk-Stimulated IP3	↓ 90%	ND
Fluid Phase Endocytosis	↑ 25%	↑ 25%
GM1	↓ 80%	unchanged

01M-0219.46 Wong



01M-0219.47 Wong

IP3 Concentration 20 Seconds After Exposure to Bradykinin



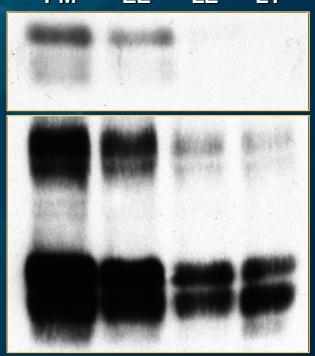
01M-0219.48 Wong

Thalamus
(Total PrP)

PM EE LE LY

Normal Hamster

Scrapie Sick Hamster

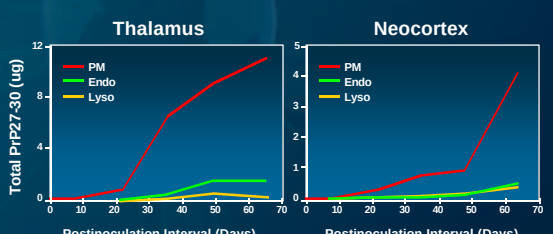


Note: Same amount of protein loaded in each lane

01M-021949 Wong

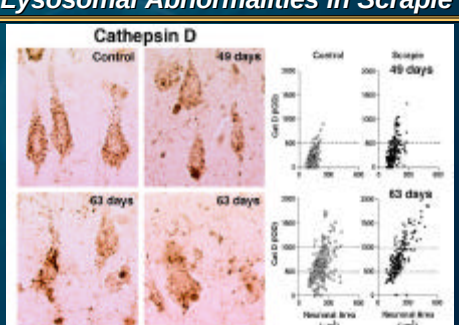
PrP27-30 Kinetics in Subcellular Fractions

Accumulation in cell membranes precedes accumulation in lysosomes by 2 to 3 weeks



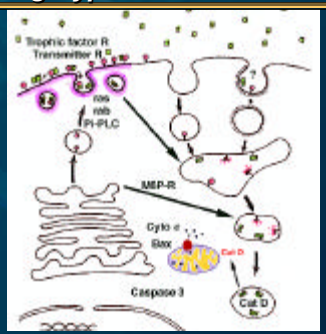
01M-021950 Wong

Lysosomal Abnormalities in Scrapie



01M-021951 Wong

Working Hypothesis



01M-021952 Wong

Human Prion Diseases

Manifestation	Disease	Mechanism
Infectious	Kuru Iatrogenic CJD Variant CJD	Transmission
Sproadic	Sporadic CJD Sporadic FI	Somatic mutation or spontaneous PrP^{C} - - - > PrP^{Sc}
Inherited	Gerstmann-Straussler-Scheinker syndrome Familial CJD Familial FI	Germline mutation

01M-021953 Wong

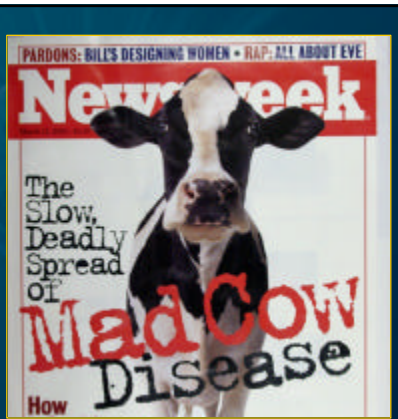
01M-021954 Wong

DENIAL:

In 1990 British Agriculture Minister John Gummer bit into a burger to allay fears about meat; six years later, infected cows were being incinerated

01M-021955 Wong

01M-021956 Wong



01M-021957 Wong


CAUTION DO NOT EAT
CAUTION


A VERY SILENT SPRING
FOOT-AND-MOUTH DISEASE RETURNS TO EUROPE